Review Article

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Aspergilloma of the brain: an overview

T. Nadkarni, A. Goel

Department of Neurosurgery, Seth G. S. Medical College, King Edward Memorial Hospital, Parel, Mumbai, India

Correspondence:
Trimurti Nadkarni,
E-mail:
tdnadkarni@hotmail.com

ABSTRACT

Fungal infections of the central nervous system (CNS) are almost always a clinical surprise. Their presentation is subtle, often without any diagnostic characteristics, and they are frequently mistaken for tuberculous meningitis, pyogenic abscess, or brain tumor. Granulocytopenia, cellular and humoral mediated immune dysfunction are predisposing factors to the development of CNS infections in immunosuppressed patients. *Aspergillus fumigatus* is the most common human pathogen in the genus Aspergillus .Maxillary sinusitis of dental origin or the lungs are the most common sites of primary Aspergillus infection. Infection reaches the brain directly from the nasal sinuses via vascular channels or is blood borne from the lungs and gastrointestinal tract. Single or multiple abscess formation with blood vessel invasion leading to thrombosis is a characteristic feature of Aspergillosis on neuropathologic examination. Aspergillosis should be considered in cases manifesting with acute onset of focal neurologic deficits resulting from a suspected vascular or space-occupying lesion especially in immunocompromised hosts. Aspergillosis is diagnosed on direct examinations and culture, however the diagnosis of aspergillosis of the CNS is difficult. Diagnosis of an intracranial mass lesion is best confirmed with a computed tomography or magnetic resonance imaging of the head with or without intravenous contrast. Aggressive neurosurgical intervention for surgical removal of Aspergillus abscesses, granulomas, and focally infracted brain; correction of underlying risk factors; Amphotericin B combined with flucytosine and treatment of the source of infection should form the mainstay of the management. Off late Liposomal Amphotericin B was found to be more effective and safe than conventional Amphotericin B in the management of Apergillus infections Only with a high index of suspicion, an aggressive approach to diagnosis, and rapid vigorous therapy may we hope to alter the clinical course in this group of patients.

KEY WORDS: *Aspergillus fumigatus*, Liposomal Amphotericin B, Fungal infections

Intracranial fungal infections are being identified more frequently due to the increased incidence of acquired immune deficiency syndrome (AIDS) patients, better radiological investigations, more sensitive microbiological techniques, and better critical care of moribund patients. General awareness of the possibility of fungal infection has also increased.

Fungi are common in the environment, but only a few are pathogenic. In general, fungi are organisms of low pathogenicity, emerging as opportunistic organisms thriving in a compromised host, however, some will infect even normal hosts. Aspergillosis is an infection of tissues or cavities by fungi of the genus *Aspergillus*. In the nervous system, the infection can be found in the cerebral parenchyma, the meninges or the vascular system.

Fungal infections of the central nervous system (CNS) are almost always a clinical surprise. Their presentation is subtle, often without any diagnostic characteristics, and they are frequently mistaken for tuberculous meningitis, pyogenic abscess, or brain tumor. Granulocytopenia, cellular and humoral mediated immune dysfunctions are predisposing factors to the development of CNS infections in immunosuppressed patients. Only with a high index of suspicion, an aggressive approach to diagnosis, and rapid vigorous therapy may we hope to alter the clinical course in this group of patients.[1]

The organism

Aspergillus fumigatus is the most common human pathogen in the genus *Aspergillus*, but *A. flavus*, *A. niger* and *A. oxyzae* are also frequently seen. They have worldwide distribution. *Aspergillus* is saprophytic opportunistic ubiquituos fungi found in soil, plants and grows as a mould on decaying vegetable matter. It has branching septate hyphae varying from 4 to 12 mm in width, which shows dichotomous branching and produces numerous spores on the tips of long conidiophores.[2]

Aspergillus fungal spores are commensal in the respiratory tract and external auditory canal. Maxillary sinusitis of dental origin or the lungs are the most common sites of primary *Aspergillus* infection. The primary portal of entry for Aspergillosis organisms is the respiratory tract. Infection reaches the brain directly from the nasal sinuses via vascular channels or is blood borne from the lungs and gastrointestinal tract. Rarely, the infection may also be air-borne contaminating the operative field during a neurosurgical procedure.[3] CNS infection has

also occurred as a complication of pituitary surgery.[4]

Disseminated aspergillosis is more common in an immunocompromised host as an opportunistic infection as seen in AIDS. CNS aspergillosis is also seen in cardiac, renal and other organ transplantation patients. It is also noted in neutropenia associated with acute leukemia and its therapy, and patients of glioblastoma multiforme on steroid therapy.[1]

Neuropathology

Single or multiple abscess formation with blood vessel invasion leading to thrombosis is a characteristic feature of Aspergillosis on neuropathologic examination. *Aspergillus* has a marked tendency to invade arteries and veins (angiotropic) producing a necrotizing angitis, secondary thrombosis, and haemorrhage. Onset of cerebral aspergillosis is heralded by manifestations of focal neurologic deficits in the anterior and middle cerebral arterial distributions. The evolving haemorrhagic infarcts convert into septic infarcts with associated abscesses and cerebritis. The fungal hyphae are found in large, intermediate and small blood vessels with invasion through vascular walls into adjacent tissue; invasion in the reverse direction can also occur. Purulent lesions may be chronic and have a tendency towards fibrosis and granuloma formation. Microscopically the most striking feature is the intensity of the vascular invasion with thrombosis. In purulent lesions, pus is seen in the centre of the abscesses with abundant polymorphs at the periphery. Granulomas consist of lymphocytes, plasma cells, and fungal hyphae.[5]

Intracranial spread of *Aspergillus* infection occurs more frequently by haematogenous routes and less frequently through direct or contiguous spread. Direct extension from the sinuses or orbit has been reported. Dissemination of the *Aspergillus* fungi to the brain from a pulmonary source occurs in 10% of patients. Direct infiltration into the basal bones leads to the more commonly encountered skull base osteomyelitis. Intracranial infection can affect the parenchyma or the meninges. According to the site and nature of infection, the patient may present with features of meningitis, focal neurological signs, or symptoms of raised intracranial pressure. The cerebral vasculature can be involved by mycotic aneurysms or intra-arterial thrombosis. *Aspergillus* hyphae can invade directly into the vessel wall, which becomes weakened due to necrosis and polymorphonuclear infiltration, resulting in mycotic aneurysm formation. These patients may present with typical subarachnoid hemorrhage syndrome. Intraluminal extension of the hyphae can also initiate thrombus formation. Rarely, major arterial stenosis may occur following leptomeningeal infection. Steroids can inhibit the macrophage response to intracellular fungus and may permit enhanced germination.

Of the 53 patients treated for fungal infection between 1967 and till date in our institution, 18 patients had a histological confirmation of the diagnosis of CNS aspergillosis. There were 12 males and six females in this group and their age ranged from 20 to 58 years (average 44 years). Two patients tested positive for human immunodeficiency virus infection. Three patients had diabetes mellitus. The lesion in four cases was in the proximity of cavernous sinus. In one case, the lesion was within the dural confines of the Meckel's cave and extended in a plexiform manner along the second division of the trigeminal nerve. In another case, the extensive basal lesion involved the paranasal sinuses, orbit, cavernous sinus, and the medial temporal brain. In the remaining 14 cases, the lesion was located within the cerebral hemisphere and presented as a large mass with extensive cerebral oedema. Seventeen patients succumbed to their disease within one year of diagnosis. One of the patients, treated with liposomal amphotericin B survived for 18 months; after which he was lost to follow-up. Autopsy was performed on 12 of these patients as they died during their hospital stay within 10 days of surgery. Ten of these patients harbored *Aspergillus* granulomas with abscesses. The brain showed evidence of meningitis and generalized cerebral edema. The intracranial vasculature in three of these patients showed *Aspergillus* invasion and secondary thrombosis. One patient had been operated for cavernous sinus *Aspergillus* granulomas. This patient died postoperatively after developing arteritis and an infarct distal to the site of surgery. Autopsy examination confirmed that fungal arteritis that led to the cerebral infarcts. Another patient had a basilar artery thrombosis and a massive posterior circulation infarction in the postoperative phase [Figure 1]. Autopsy study and examination of the basilar artery confirmed the presence of *Aspergillus* fungus within the artery and thrombosis of the vessel.

Clinical manifestations

Aspergillosis should be considered in cases manifesting with acute onset of focal neurologic deficits resulting from a suspected vascular or space-occupying lesions especially in immunocompromised hosts. In patients with paranasal sinus disease, orbital extension with proptosis, ocular palsies, visual deterioration, and chemosis may occur. The symptoms frequently encountered are headache, vomiting, convulsions, hemiparesis, fever, cranial nerve deficits, paralysis, and sensory impairment of varying degree. Features typical of meningitis and subarachnoid hemorrhage resulting from mycotic aneurysms may manifest.[1],[2],[5]

Patients are often afebrile or have only a low-grade fever. Their symptoms are usually those of a cerebral mass lesion, although the propensity of the fungus to invade blood vessels may lead to extensive necrosis and sometimes to intracranial bleeding.[6]

The disease is usually slowly progressive and symptoms may persist for months. Brainstem or cerebellar signs were the presenting features in one series of 11 patients, in which rapid neurologic deterioration and death occurred in nine patients.[1]

Goel *et al*.[7] have reported aspergilloma to involve the Gasserian ganglion in two healthy individuals. These paracavernous tumors mimicked a meningioma and a trigeminal neurinoma on preoperative imaging and intraoperative consistency and vascularity. The lesions were successfully and completely resected. Both patients developed major cerebral arterial territory infarcts in the postoperative phase, remote from the site

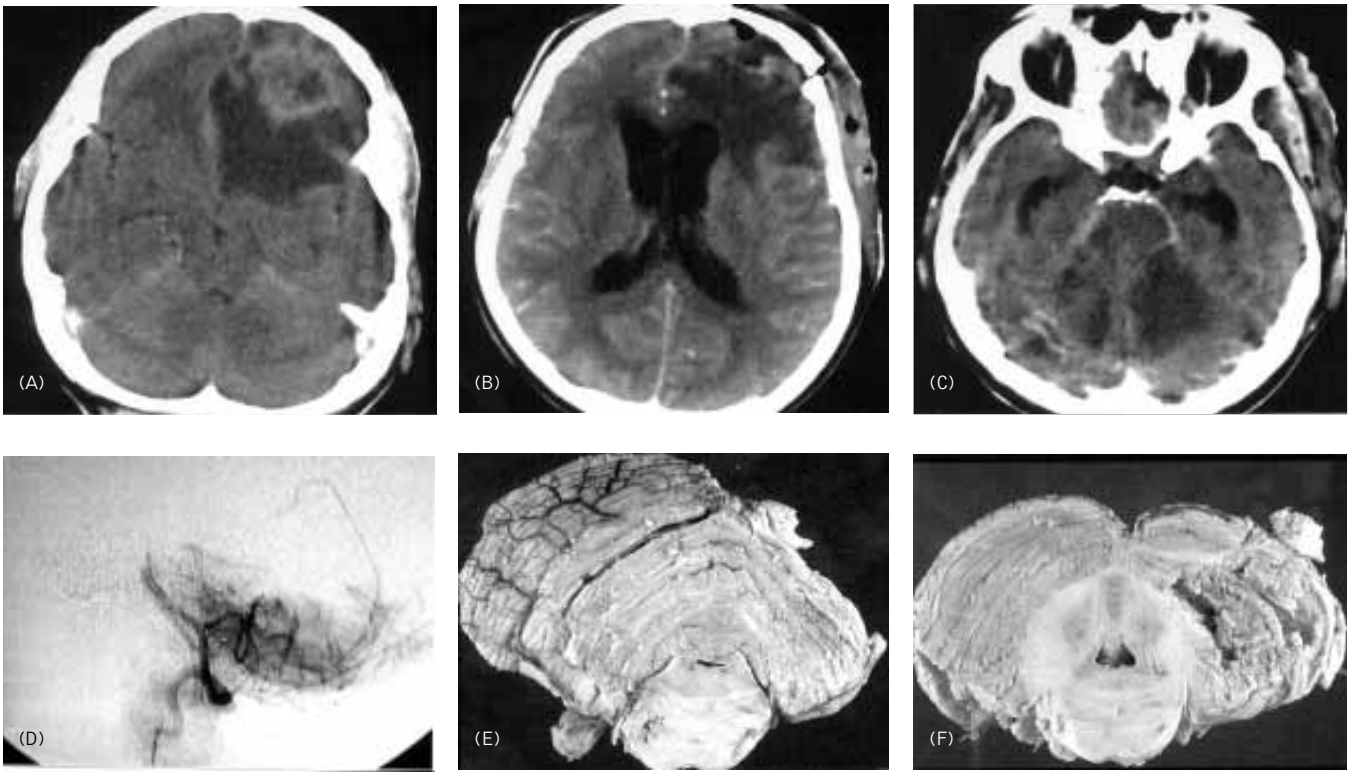

Figure 1: (A) Postcontrast axial CT scan shows a left frontal *Aspergillus* granuloma. (B) Postoperative CT scan shows excision of left frontal granuloma by a left frontal craniotomy. (C) Postoperative CT scan shows bilateral cerebellar and brainstem infarcts noted as hypointense areas. (D) Vertebral angiogram demonstrates complete occlusion of basilar artery. (E) Axial cut section of the postmortem specimen of the brain shows a brainstem infarct. (F) A section taken inferiorly shows a cerebellar infarct

of the operation, leading to crippling neurological deficits in one patient, and death in the other. Nadkarni *et al*.[8] have reported a similar clinical course in a 32-year-old male with paranasal sinus infection with intracranial extension. This patient succumbed to a basilar artery thrombosis following a left frontal granuloma excision [Figure 1]. These cases highlight the unusual location of intracranial aspergilloma and the possibility of ischaemic complications after surgical resection of intracranial aspergilloma.

Investigations

Aspergillosis is diagnosed on direct examinations and culture, however, the diagnosis of aspergillosis of the CNS is difficult.

Spinal fluid findings

In general, lumbar puncture is contraindicated in patients with intracranial mass lesions with associated cerebral oedema. Altering the intracranial pressure by withdrawing spinal fluid for laboratory examination may precipitate a cerebral herniation syndrome or abscess rupture into the ventricular system.

Spinal fluid pleocytosis (600 cells/mm^3) and moderately elevated CSF proteins are present, but CSF glucose is usually normal in CNS Aspergillosis. There are many exceptions to this picture and virtually any CSF response can occasionally be seen, including a normal spinal fluid. Organisms are rarely found in CSF. The characteristic branching sepatate hyphae and conidia of *Aspergillus* species are faintly visible with H & E stain and periodic acid-Schiff (PAS) reagent but are most readily seen with Gomori's methenamine silver (GMS) stains. Potassium hydroxide wet preparations can demonstrate *Aspergillus*. Red blood cells may be seen in the CSF of patients with CNS aspergillosis.[1],[2]

Neuroradiology [Figures 2 and 3]

Diagnosis of an intracranial mass lesion is best confirmed with a computed tomography (CT) or magnetic resonance (MR) imaging of the head with or without intravenous contrast. On CT low-density lesions that may or may not enhance with contrast can represent fungal abscesses. Chronic abscesses have demonstrated ring and homogenous enhancement. Minimal mass effect, low absorption areas, and slight or no contrast enhancement were seen on CT in patients with A. *fumigatus* brain abscess. Increased sensitivity of the MR imaging scan can be useful for demonstrating multiple small intracerebral abscesses not apparent on CT, whereas CT scanning provides a convenient way to monitor a patient's response to antimicrobial therapy.

Culture

Aspergillus cultured optimally on Sabourad's agar demonstrates characteristic conidiophores. However, blood and cerebrospinal fluid cultures, even in disseminated disease, are frequently negative.

Serologic tests

Serial serologic tests (i.e. double diffusion counterimmuno-

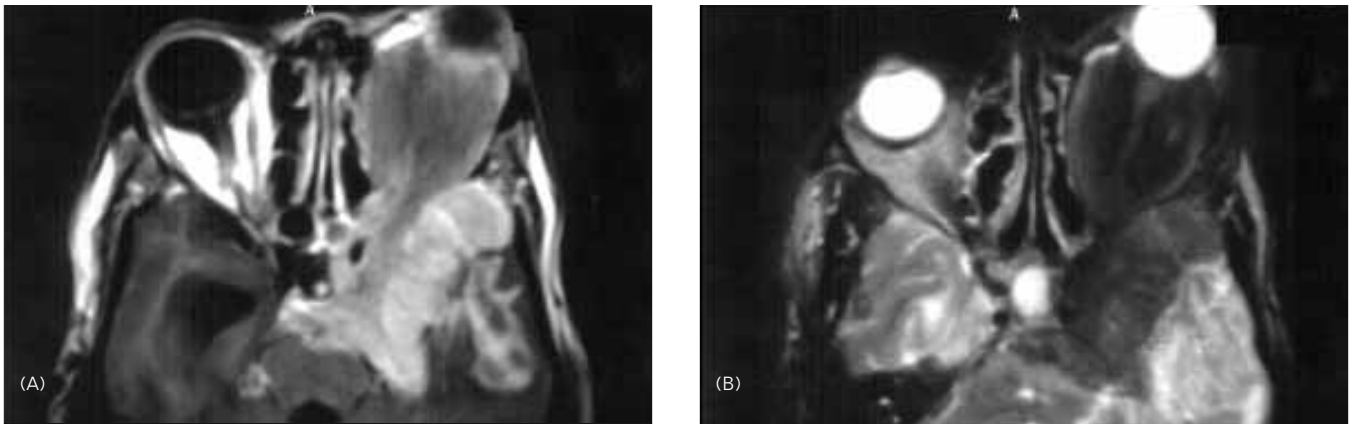

Figure 2: (A) PostGadolinium MR axial image that shows an enhancing mass extending from the orbit into the cranium. The mass invades into the ethmoid sinuses, cavernous sinus, sphenoid sinus, and middle cranial fossa. The internal carotid and basilar arteries are encased in the inflammatory tumor. The temporal brain has been infiltrated. (B) T2-weighted axial MR image shows that the mass is hypointense, typical of an inflammatory granuloma. Histologically this tumor was an aspergilloma

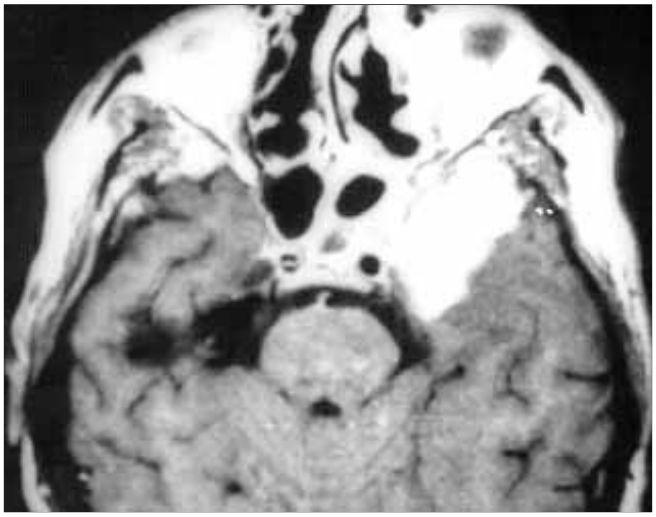

Figure 3: PostGadolinium MR axial image shows an enhancing cavernous sinus mass. The mucosas of the sphenoid and ethmoid sinuses are thickened and enhancing. Histology confirmed the mass to be an aspergilloma

electrophoresis, immunofluorescence, or enzyme-linked immunosorbent assay) significantly help in arriving at a diagnosis. Immunoasssay may detect the disease early but these tests are rarely done. Serologic testing has been unreliable for A. *fumigatus*, except in leukemia patients followed prospectively.

Therapy

Aggressive neurosurgical intervention for surgical removal of *Aspergillus* abscesses, granulomas, and focally infarcted brain, correction of underlying risk factors. Amphotericin B combined with flucytosine and treatment of the source of infection should form the mainstay of the management.

Surgical debridement enhances abscess penetration by removal of necrotic debris. Radical surgical debridement can be curative in *Aspergillus* brain abscess if the extent of resection extends into uninvolved tissue. Lobectomy in patients with a single A. *fumigatus* abscess is an acceptable surgical option when noneloquent areas of the brain are involved. In four of seven patients with cerebral aspergillosis, who survived, complete surgical resection of brain abscess was accomplished.[9]

Stereotactic aspiration is the procedure of choice for most brain abscesses, particularly those measuring more than 1.5 cm. Indications for aspiration include to aid in the diagnosis, to relieve mass effect, to improve the efficacy of drug treatment and it is also used when systemic therapy appears to be ineffective for a presumed organism. Complete aspiration of an abscess is not necessary and can predispose to haemorrhage into the evacuated cavity. Stereotactic drainage or biopsy and systemic, intraventricular or intraocular administration of amphotericin B has been effective in *Aspergillus* abscesses.[1]

Amphotericin B has been the mainstay of therapy for the past quarter century. An intravenous test dose of 1 mg or 0.1 mg/kg infused over 30 min to rule out anaphylaxis (occurring in 1% of cases) is recommended. The dose is increased from 0.25 to 1.5 mg/kg as once daily intravenous infusion given over 2–4 h. How ever, its use is limited by its toxic effects. To reduce the toxicity of amphotericin B, liposomal amphotericin B and its combination with lipids have been introduced. All major advantages of these lipid formulations of amphotericin B are a reduction in two forms of toxicity, which include infusion-related toxicities and nephrotoxicity. In India, Bacchawat and coworkers had developed liposomal amphotericin, which was modified by Kshirsagar *et al*. to patient-worthy, sterile pyrogen free preparations. The same group studied different dosage regimens of liposomal amphotericin in *Aspergillus* model and found that liposomal amphotericin was more effective than equal dose of free amphotericin B. Subsequent clinical trial with Indian Liposomal amphotericin B (Fungisome™) have demonstrated the safety and efficacy in treatment of CNS aspergilloma.[10]–[12] This indigenous preparation is significantly cost-effective when compared to similar preparations. Out of the seven patients treated with indigenous liposomal ampho-

tericin B, four had complete response, one had partial response and two had no response.[13] Because of poor penetration into the CSF, when given systemically, direct instillation of amphotericin B into an abscess cavity through an indwelling catheter has also been advocated.[14] Combination therapy with 5-fluorocytosine has also been recommended. Rifampicin and 5-fluorocytosine may act synergistically with amphotericin B in CNS fungal disease. The dose of flucytosine is 50–150 mg/kg/day given orally at 6-hourly intervals. Itraconazole (oral 200 mg od), miconazole (infusion of 0.2–1.2 g thrice daily), and sulfamethoxazole have also been effective. These drugs were used to control the spread of the disease and were not curative.

Whenever possible, immunosuppressive therapy should be lowered or discontinued in the compromised host with CNS infection. Unfortunately, rejection is often concomitant with infection, requiring higher doses of immunosuppressive agents. In patients with cancer, systemic disease is frequently stable because of continuing chemotherapy when CNS infection develops.

Ischaemic complications after surgical resection of intracranial Aspergillomas[7],[8]

The postoperative phase of patients operated for *Aspergillus* infections of the brain is marred by major cerebral arterial territory infarcts remote from the site of infection, leading to crippling neurological deficits and even death. Histological infection has shown fungal hyphae within the wall of the involved arteries. The stress of surgery and the use of steroids to control cerebral edema in the immediate postoperative phase may have been contributory factors in the fungal growth.

High awareness of the possibilities of fungal infection on the basis of radiology or operative findings, avoidance of steroids, and early treatment with antifungal agents may help to prevent such a vascular insult.

Prognosis

The prognosis for CNS aspergillosis is poor, with most reported cases being fatal. Fungal abscesses in patients with cancer are usually fatal.[15] An aggressive surgical approach in nonimmunocompromised patients helped to reduce the mortality form 64 to 39%.[16] Intracerebral aspergillosis is frequently fatal in immunocompromised patients, with only 12 reported cases of successful treatment.[13]

Because many immunocompromised patients have had years of productive life before developing CNS infection, rapid diagnosis and effective medical and surgical treatments are essential to preserve neurologic function and assure a good quality of life.

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